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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 05/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/865,281	KOHLER, HEINZ	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *1-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-40 are pending.

2. Claims 1-20 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

3. In view of the amendment filed 3/7/06, the following rejections remain.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 22-25, 27-31, and 33-35 stands rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an antigen-binding fusion protein comprising an antibody and a peptide of SEQ ID NO: 1 having homophilic activity wherein the antibody is a murine anti-idiotypic antibody 3H1 that mimics carcinoembryonic antigen (CEA) and the peptide is a complement C3d fragment that binds to complement receptor on B cells and wherein the peptide does not interfere with antibody binding, (2) the said fusion protein wherein the antibody is a full-length immunoglobulin or an antigen binding fragment thereof, (3) the said antigen-binding fusion protein wherein said peptide has inverse hydropathicity within the length of said peptide, (4) the said antigen-binding fusion protein wherein said antibody comprises a light chain *and* a heavy chain immunoglobulin and wherein said peptide is localized internally to said light chain or heavy chain immunoglobulin molecule, (4) an antigen-binding fusion protein comprising an antibody and a peptide of SEQ ID NO: 1 having immuno-stimulatory activity wherein the antibody is a murine anti-idiotypic antibody 3H1 and the peptide is a complement C3d fragment that binds to complement receptor on B cells, wherein the peptide does not interfere with antibody binding, and wherein said antibody comprises a light chain and heavy chain immunoglobulin molecule and wherein said peptide is attached to the C-terminal or the N-terminal of said light chain or heavy chain immunoglobulin molecule, (5) the said antigen-binding fusion protein wherein said peptide is derived from the human C3d residues at position 1217-1232, (5) an antigen-binding fusion protein comprising an antibody and a peptide of SEQ

ID NO: 1 having membrane transport activity wherein the antibody is a murine anti-idiotypic antibody 3H1 that mimics the carcinoembryonic antigen (CEA) and the peptide is a complement C3d fragment that binds to complement receptor on B cells and wherein said peptide does not interfere with antibody binding, **does not** reasonably provide enablement for any fusion protein as set forth in claims 22-25, 27, 28-31, and 33-35. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only anti-idiotypic antibody 3H1 that induces anti-CEA antibody fused to a peptide consisting of SEQ ID NO: 1 which derived from human C3d region 1217-1232 that binds to the CR2 receptor on B cells and enhance the immunogenicity of the anti-idiotypic antibody that was used as CEA antigen (See page 15-16). The only peptide that has homophilic, immunostimulatory and membrane transport is peptide of SEQ ID NO: 1 derived from C3d region 1217-1232 of human C3d. The specification does not teach any other peptide, much less which peptide is a homolog or non-human C3d peptide (see page 12-13 of specification). The specification discloses fusing C3d peptide as adjuvant to hen egg lysozyme (HEL) to enhance the immunogenicity of the immunogen HEL. The HEL immunogen is not an antibody.

The specification does not teach how to make and use any antigen-binding fusion protein as set forth in claims 22, 27, 28, 30, 33 and 34 because antibody that binds an antigen requires both light chain and heavy chain. There is a lack of guidance and working example demonstrating that antibody comprises either light chain or heavy chain is capable of binding. The state of the antibody art as exemplified by Harlow et al, of record, is such that antibody binding to antigen requires *both* the variable domains of heavy *and* light chains to form an

antigen binding site (see page 8-9, Figure, in particular). Note, amending claims 22, 27, 28, 30, 33 and 34 to recite "...a light chain and heavy chain..." would obviate this rejection.

With respect to the issue in claim 23, the specification does not teach any and all antibody, much less any nucleic acid encoding any antibody without the nucleic acid sequence. The term "a nucleic sequence encoding **an** antibody and a nucleic acid sequence encoding said peptide" at line 8-9 of claim 23 encompasses any nucleic acid encoding any antibody, not the specific anti-idiotype antibody 3H1 in the fusion protein. Given the lack of guidance as to the structure of the antigen, and binding specificity of all antibody in the claimed fusion protein, one of skill in the art cannot make, much less use the claimed invention. Accordingly, it would require undue experimentation of one skilled in the art to practice the claimed invention.

With respect to the issue in claims 24 and 35, the specification discloses murine anti-idiotypic antibody 3H1 that mimics carcinoembryonic antigen (CEA), the specification does not disclose said antibody is specific for any cellular receptor on a normal cell or on a tumor cell, see page 24 of specification.

With regard to "a variable domain containing fragment of an antibody" in claim 25, there is insufficient guidance as to the structure of the fragment without the amino acid sequence. Further, it is not clear which variable domain fragment and from which antibody since the term "an antibody" encompasses any antibody. It is well known in the art at the time the invention was made that a single variable domain fragment does not bind to any antigen, see Harlow et al, of record. Note, amending the claim to recite "...or an antigen binding fragment thereof." would obviate this rejection.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 3/26/06 have been fully considered but are not found persuasive.

Applicants' position is that claims have been amended. The invention as presently claimed is directed to an antigen-binding fusion protein comprising an antibody and a peptide possessing homophilic, immuno-stimulatory and/or membrane transport activities. Applicant respectfully points out that the present invention is a fusion protein comprising an anti-idiotypic anti-CEA antibody fused to a peptide of SEQ ID NO: 1 derived from the C3d region 1217-1232.

In response, the specification discloses only anti-idiotypic antibody 3H1 that induces anti-CEA antibody fused to a peptide consisting of SEQ ID NO: 1 which derived from human C3d region 1217-1232 that binds to the CR2 receptor on B cells and enhance the immunogenicity of the anti-idiotypic antibody that was used as CEA antigen (See page 15-16). The only peptide that has homophilic, immunostimulatory and membrane transport is peptide derived from C3d region 1217-1232 of human C3d. The specification does not teach any other peptide, much less which peptide is a homolog or non-human C3d peptide (see page 12-13 of specification). The specification discloses fusing C3d peptide as adjuvant to hen egg lysozyme (HEL) to enhance the immunogenicity of the immunogen HEL. The HEL immunogen is not an antibody.

The specification does not teach how to make and use any antigen-binding fusion protein as set forth in claims 22, 27, 28, 30, 33 and 34 because antibody that binds an antigen requires both light chain and heavy chain. There is a lack of guidance and working example demonstrating that antibody comprises either light chain or heavy chain is capable of binding. The state of the antibody art as exemplified by Harlow et al, of record, is such that antibody binding to antigen requires *both* the variable domains of heavy *and* light chains to form an antigen binding site (see page 8-9, Figure, in particular). Note, amending claims 22, 27, 28, 30, 33 and 34 to recite "...a light chain and heavy chain..." would obviate this rejection.

With respect to the issue in claim 23, the specification does not teach any and all antibody, much less any nucleic acid encoding any antibody without the nucleic acid sequence. The term "a nucleic sequence encoding **an** antibody and a nucleic acid sequence encoding said peptide" at line 8-9 of claim 23 encompasses any nucleic acid encoding any antibody, not the specific anti-idiotype antibody 3H1 in the fusion protein. Given the lack of guidance as to the structure of the antigen, and binding specificity of all antibody in the claimed fusion protein, one of skill in the art cannot make, much less use the claimed invention. Accordingly, it would require undue experimentation of one skilled in the art to practice the claimed invention.

With respect to the issue in claims 24 and 35, the specification discloses murine anti-idiotypic antibody 3H1 that mimics carcinoembryonic antigen (CEA), the specification does not

disclose said antibody is specific for any cellular receptor on a normal cell or on a tumor cell, see page 24 of specification.

With regard to "a variable domain containing fragment of an antibody" in claim 25, there is insufficient guidance as to the structure of the fragment without the amino acid sequence. Further, it is not clear which variable domain fragment and from which antibody since the term "an antibody" encompasses any antibody. It is well known in the art at the time the invention was made that a single variable domain fragment does not bind to any antigen, see Harlow et al, of record. Note, amending the claim to recite "...or an antigen binding fragment thereof." would obviate this rejection.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

6. Claims 22-25, 27-31, and 33-35 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of any and all antibody and any nucleic acid sequence encoding any antibody fused to any nucleic acid encoding a peptide of SEQ ID NO: 1.

The specification discloses only anti-idiotypic antibody 3H1 that induces anti-CEA antibody fused to a peptide consisting of SEQ ID NO: 1 which derived from human C3d region 1217-1232 that binds to the CR2 receptor on B cells and enhance the immunogenicity of the anti-idiotypic antibody that was used as CEA antigen (See page 15-16). The only peptide that has homophilic, immunostimulatory and membrane transport is peptide derived from C3d region 1217-1232 of human C3d. The specification does not teach any other peptide, much less which peptide is a homolog or non-human C3d peptide (see page 12-13 of specification). The specification discloses fusing C3d peptide as adjuvant to hen egg lysozyme (HEL) to enhance the immunogenicity of the immunogen HEL. The HEL immunogen is not an antibody.

The specification does not disclose any and all antibody, much less any nucleic acid encoding any antibody without the nucleic acid sequence (claim 23). The term "a nucleic sequence encoding **an** antibody and a nucleic acid sequence encoding said peptide" at line 8-9 of

claim 23 encompasses any nucleic acid encoding any antibody, not the specific anti-idiotype antibody 3H1 in the fusion protein.

The specification does not teach adequately describe the antibody in the any antigen-binding fusion protein as set forth in claims 22, 27, 28, 30, 33 and 34 because antibody that binds an antigen requires both light chain and heavy chain. Since the antibody comprising a light chain, then the heavy chain of the antibody in the claimed antigen-binding fusion protein is not adequately described. Likewise, the antibody comprising only the heavy chain, then the light chain of the antibody in the claimed antigen-binding fusion protein is not adequately described. Note, amending the claim to recite "...antibody comprises a light chain *and* a heavy chain..." would obviate this rejection.

With respect to the issue in claims 24 and 35, the specification discloses murine anti-idiotypic antibody 3H1 that mimics carcinoembryonic antigen (CEA), the specification does not disclose said antibody is specific for any cellular receptor on a normal cell or on a tumor cell, see page 24 of specification.

With regard to "a variable domain containing fragment of an antibody" in claim 25, there is inadequate written description about the fragment without the amino acid sequence. Further, it is not clear which variable domain fragment, i.e. CDR1 through 3 from heavy or light chain and from which antibody since the term "an antibody" encompasses any antibody. Note, amending the claim to recite "...or an antigen binding fragment thereof." would obviate this rejection.

Finally, given the lack of an additional species of antibody that binds to any cellular receptor on normal or tumor cell and any nucleic acid encoding any antibody, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 3/7/06 have been fully considered but are not found persuasive.

Applicants' position is that claims have been amended. The invention as presently claimed is directed to an antigen-binding fusion protein comprising an antibody and a peptide

possessing homophilic, immuno-stimulatory and/or membrane transport activities. Applicant respectfully points out that the present invention is a fusion protein comprising an anti-idiotypic anti-CEA antibody fused to a peptide of SEQ ID NO: 1 derived from the C3d region 1217-1232.

In response, the specification does not disclose any and all antibody, much less any nucleic acid encoding any antibody without the nucleic acid sequence (claim 23). The term "a nucleic sequence encoding **an** antibody and a nucleic acid sequence encoding said peptide" at line 8-9 of claim 23 encompasses any nucleic acid encoding any antibody, not the specific anti-idiotype antibody 3H1 in the fusion protein.

The specification does not teach adequately describe the antibody in the any antigen-binding fusion protein as set forth in claims 22, 27, 28, 30, 33 and 34 because antibody that binds an antigen requires both light chain and heavy chain. Since the antibody comprising a light chain, then the heavy chain of the antibody in the claimed antigen-binding fusion protein is not adequately described. Likewise, the antibody comprising only the heavy chain, then the light chain of the antibody in the claimed antigen-binding fusion protein is not adequately described. Note, amending the claim to recite "...antibody comprises a light chain *and* a heavy chain..." would obviate this rejection.

With respect to the issue in claims 24 and 35, the specification discloses murine anti-idiotypic antibody 3H1 that mimics carcinoembryonic antigen (CEA), the specification does not disclose said antibody is specific for any cellular receptor on a normal cell or on a tumor cell, see page 24 of specification.

With regard to "a variable domain containing fragment of an antibody" in claim 25, there is inadequate written description about the fragment without the amino acid sequence. Further, it is not clear which variable domain fragment, i.e. CDR1 through 3 from heavy or light chain and from which antibody since the term "an antibody" encompasses any antibody. Note, amending the claim to recite "...or an antigen binding fragment thereof." would obviate this rejection.

Finally, given the lack of an additional species of antibody that binds to any cellular receptor on normal or tumor cell and any nucleic acid encoding any antibody, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

7. The following new grounds of rejections are necessitated by the amendment filed 3/7/06.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 21-40 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

"An antigen-binding fusion protein ...wherein the antibody is specific for cellular receptor ...wherein the antibody is a murine anti-idiotypic antibody 3H1..." in Claims 21, 23, 28 and 32 represents a departure from the specification and the claims as originally filed.

This is because anti-idiotypic antibody 3H1 mimics carcinoembryonic antigen (CEA) and does not bind to any receptor, see specification at page 24.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

11. Claims 21-24, and 27-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "...wherein the antibody is specific for cellular receptor and the peptide is a specific binding site derived from a natural ligand for a specific cellular receptor..." in the n antigen-binding fusion protein as set forth in claims 21, 23, and 28 and is indefinite and ambiguous because the binding specificity of the antibody in the fusion protein is not clear. Further, the peptide is derived from which natural ligand for which cellular receptor ? One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

The "...antibody is specific for a cellular receptor on a normal cell or on a tumor cell" in claims 24, 31, and 35 is indefinite because anti-idiotype antibody 3H1 binds to CEA on tumor cell, not a cellular receptor on a normal cell or on a tumor cell.

The "non-human C3d region homologous to the human C3d to the human C3d residues at position 1217-1232" in claims 29, 36, 37, 38, 39 and 40 is indefinite and ambiguous because the 16-mer peptide of SEQ ID NO: 1 is derived from human C3d residues at position 1217-1232, not from any human homolog. One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

The "ranges from about 10 to about 16 mer" in claim 39 has no antecedent basis in base claim 32 because the peptide of SEQ ID NO: 1 is a 16mer and now the peptide in the dependent claim becomes longer than 16 amino acids.

The "...antibody comprises a light chain *or* heavy chain..." in claims 22, 27, 28, 30, 33, and 34 is indefinite because antibody requires both light chain *and* heavy chain of an immunoglobulin to bind to an antigen. One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

12. No claim is allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone

are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

15. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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